

**EUROPEAN PATENT APPLICATION**

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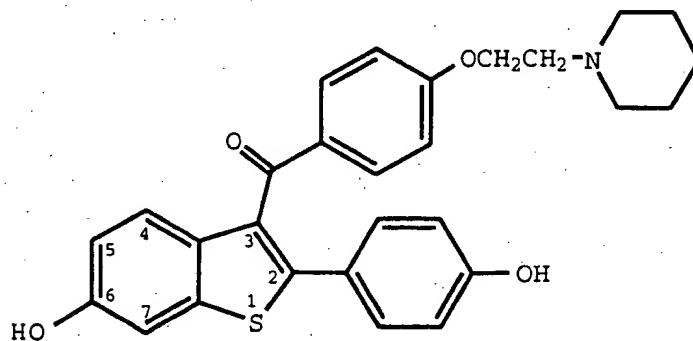
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⑤4 Ralocifene for inhibiting fertility in women.

(57) A method of inhibiting fertility in women comprising administering to a female human an effective amount of a compound having the formula



(I)

and pharmaceutically acceptable salts and solvates thereof.

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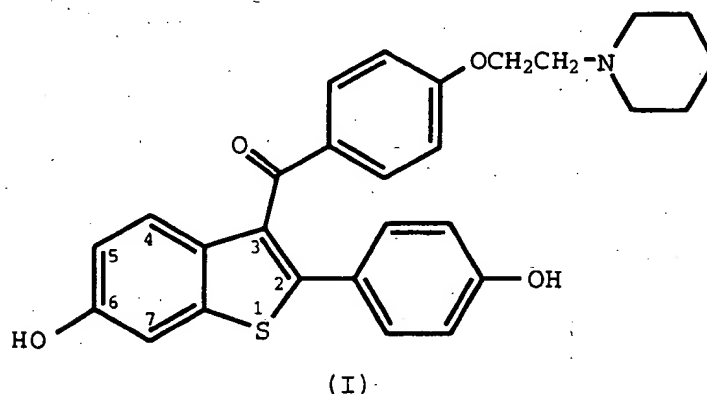
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54 **Raloncifene for inhibiting fertility in women.**

57 A method of inhibiting fertility in women comprising administering to a female human an effective amount of a compound having the formula



and pharmaceutically acceptable salts and solvates thereof.

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Contraceptive methods involving the administration of chemical substances are widely practiced among women who desire to limit pregnancies. Such methods control fertility through various biological mechanisms. Among the presently used chemical methods of fertility control, the most important are those which act by means of the following: (a) suppression of ovulation through inhibition of gonadotropin release; (b) alteration of the female reproductive tract to prevent migration of sperm to the site of fertilization or, if fertilization occurs, to block implantation of the zygote (nidation); (c) spermicidal action or (d) an abortifacient.

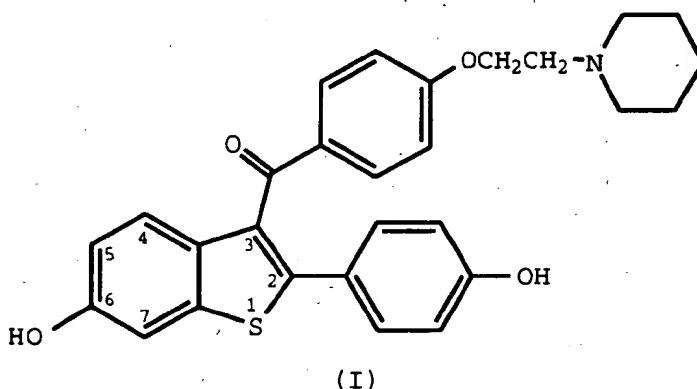
The oral contraceptives are the most prominent chemical contraceptive agents. Two types of agents are (a) estrogen combined with a progestin, and (b) a progestin alone. The contraceptives of the combined type act primarily by suppressing ovulation by negative feedback to prevent gonadotropin (LH and FSH) release by the hypothalamus, but alterations in the reproductive tract may also contribute to the antifertility effect. Such alterations include changes in the cervical mucus (which increase the difficulty of sperm migration) and in the endometrium (which decrease the likelihood of nidation). The action of a progestin alone in a very low oral dose ("mini-pill") appears to involve primarily alterations in the female reproductive tract, but ovulation suppression may also occur. Although the oral contraceptives are highly effective, their use is associated with unpleasant side effects (such as nausea, depression, weight-gain, and headache) and an increased long-time risk of severe disease (such as thromboembolism, stroke, myocardial infarction, hepatic adenoma, gall bladder disease, and hypertension). Bleeding irregularities (such as break-through bleeding, spotting, and amenorrhea) are also frequent. A progestin, when administered alone, causes an increased incidence of changes in menstrual patterns, especially a marked increase in the amount and duration of menstrual bleeding.

Other chemical methods of contraception include the post coital administration of estrogens (e.g. diethylstilbestrol, antiprogestins, or ethynylestradiol) to prevent nidation or of prostaglandins which act as abortifacients. Both of these methods, at present, are limited to emergency situations. Still in the very early stages of development are immunological methods (vaccination) and methods involving the direct control of LHRH secretion from the pituitary by LHRH agonists or antagonists.

Another group of chemical contraceptive agents are the local spermicides, such as nonoxynol or octoxynol, which are placed into the vagina immediately prior to coitus in the form of creams, foams, jellies, or suppositories. The spermicidal action takes place either in the vagina or elsewhere in the reproductive tract. For the latter to occur, the spermicidal agent is either absorbed on sperm membranes or is transported into the uterus under the influence of uterine contractions. The spermicidal methods are not completely reliable in preventing pregnancy and are inconvenient to use.

From the foregoing, it is evident that the presently available methods of contraception are inadequate for various reasons. Although many women practice contraception in spite of these inadequacies, a need exists in medicine for new methods.

This invention provides methods for inhibiting fertility in women comprising administering to a female human an effective amount of a compound of formula I



and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that compounds of formula I are useful for inhibiting fertility in women. The methods of treatment provided by this invention are practiced by administering to a female human a dose of raloxifene or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit fertility. The term inhibit fertility includes reducing fertility and further includes reducing the likelihood of a woman being able to give birth during the period of administration, and for a time thereafter. It includes any period

of time in which fertility is decreased. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

Raloxifene, which is the hydrochloride salt of the compound of formula 1, has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and pharmacology was that of an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other cell types, raloxifene activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although raloxifene and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not easily predicted and is unique to each.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally or intravaginally, and may be formulated as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The hydroxyl groups of the starting compound are protected, the three position is acylated, and the product deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate,  $\beta$ -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycolate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as qua-

ternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit fertility in women according to this invention will depend upon the patient's physical characteristics, the route of administration, and related factors that will be evaluated by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject from once to about three times each day.

It is also advantageous to administer a compound by the oral route. For such purposes the following oral dosage forms are available.

#### Formulations

##### Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Raloxifene	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of capsule formulations include those shown below:

##### Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

**Formulation 3: Raloxifene capsule**

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

**Formulation 4: Raloxifene capsule**

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

**Formulation 5: Raloxifene capsule**

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.  
A tablet formulation is prepared using the ingredients below:

**Formulation 6: Tablets**

Ingredient	Quantity (mg/tablet)
Raloxifene	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

**Formulation 7: Tablets**

	Ingredient	Quantity (mg/tablet)
5	Raloxifene	0.1 - 1000
	Starch	45
	Cellulose, microcrystalline	35
10	Polyvinylpyrrolidone (as 10% solution in water)	4
	Sodium carboxymethyl cellulose	4.5
	Magnesium stearate	0.5
15	Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

**Formulation 8: Suspensions**

	Ingredient	Quantity (mg/5 ml)
30	Raloxifene	0.1 - 1000 mg
	Sodium carboxymethyl cellulose	50 mg
	Syrup	1.25 mg
35	Benzoic acid solution	0.10 mL
	Flavor	q.v.
	Color	q.v.
40	Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

**TEST PROCEDURES****ASSAY 1**

Between five and fifty young adult virgin female rats weighing 200-230 g. each are separated into groups having the same number of rats.. One of the groups serves as the control group and the other groups as experimental groups, each such experimental group receiving raloxifene at a particular dose level. Raloxifene is prepared in corn oil such that the daily administration is in 0.1 ml. of vehicle. The designated quantity of raloxifene in the vehicle is administered to each rat within the defined group subcutaneously (sc) daily. Alternatively, administration may be made via oral gavage or an intramuscular route. The control group receives only the vehicle. Administration of the vehicle or the combination of raloxifene and vehicle is continued on a daily basis for 15 days. On the 5th day of treatment, one or two adult male rats weighing at least 250 g. are added to each group, and cohabitation is continued until the 15th day at which time the male rats are withdrawn

from the group. Each group of female rats then is maintained for an additional seven days after which the rats are sacrificed and examined for the presence of viable or resorbing fetuses.

The number of animals that exhibit evidence of pregnancy over the number of animals in the group multiplied by one hundred is the pregnancy ratio percentage (PRP). A compound is considered active when the PRP is 0 to 20%. A PRP of 40% constitutes marginal activity, and anything higher is inactive.

## ASSAY 2

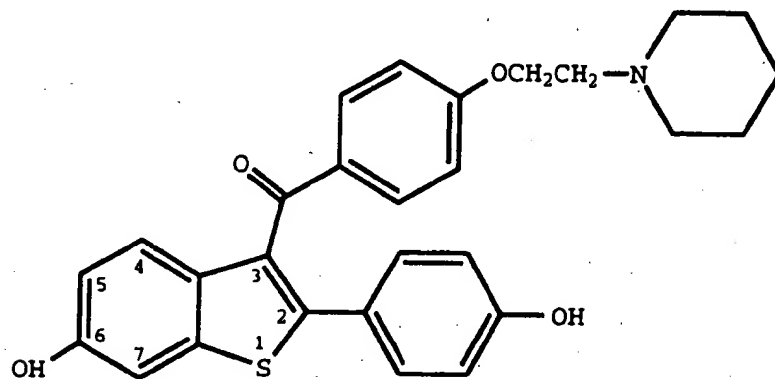
Between five and fifty young adult virgin female rats weighing 200-230 g. each are separated into groups having the same number of female rats, and paired with male rats. One of the groups serves as the control group and the other groups as experimental groups. Vaginal Smears are performed on the females daily until sperm and vaginal plugs are found, which coincides with the day of vaginal estrus and is designated day one of pregnancy.

The male rats are removed, and the experimental groups of female rats are administered raloxifene via oral gavage, an intramuscular route, or by subcutaneous injection. The administration continues on a daily basis until the twelfth day of pregnancy at which time all the female rats are sacrificed and examined for the presence of implantation sites. A compound is considered active when the PRP, as defined above, is 60% or lower.

Utility of the compounds described herein is exhibited by activity in at least one of the above assays.

## Claims

1. The use of a compound having the formula



(I)

or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting fertility in women.

2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.
3. The use of Claim 1 wherein said medicament is prophylactic.





European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number  
EP 94 30 9487

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	EP-A-0 062 505 (ELI LILLY) 13 October 1982 * abstract * * page 6, line 1 - line 10; claims; examples * ---	1-3	A61K31/445 A61K31/40 A61K31/38
D,Y	US-A-4 133 814 (JONES ET AL.) 9 January 1979 * abstract * * column 2, line 5 - column 3, line 60; claims; table I * ---	1-3	
Y	DRUGS OF THE FUTURE, vol. VII, no.2, 1981 pages 112-113, 'LY-117,018' * the whole document * ---	1-3	
Y	REPRODUCTIVE TOXICOLOGY, vol. 6, no.5, 1992 pages 439-446, Y-C. CHOU ET AL. 'EFFECTS OF ANTIESTROGENS ON ADULT AND NEONATAL MOUSE REPRODUCTIVE ORGANS' * the whole document * ---	1-3	
D,Y	US-A-4 418 068 (JONES) 29 November 1983 * abstract; claims * -----	1-3	
The present search report has been drawn up for all claims			
Place of search <b>THE HAGUE</b>		Date of completion of the search <b>23 March 1995</b>	Searcher <b>Hoff, P</b>
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document</p>			

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